Editorial

Myc and Ras, the Bonnie and Clyde of immune evasion

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Topper MJ, Vaz M, Chiappinelli KB, *et al.* Epigenetic Therapy Ties MYC Depletion to Reversing Immune Evasion and Treating Lung Cancer. Cell 2017;171:1284-300.e21.

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The ability of different oncogenes to cooperate effectively with each other in promoting tumor growth has long been a major focus of research. Until recently it was thought that oncogenes, including *Ras* and *Myc*, contributed to tumor proliferation and survival only through tumor cell-intrinsic mechanisms. However, it is now evident that oncogenes not only drive relentless cell division and corollary intracellular programs, but also contribute to the instruction of the tumor microenvironment. The latter is intimately related to immune evasion—the mechanism through which cancer cells avoid host immune surveillance mechanisms—by inducing an immunosuppressive microenvironment and immune edition.

In this context, a recent publication by Kortlever *et al.* has shed significant light on a new aspect of oncogenic cooperation between KRas and Myc. Indeed, making use of a non-small cell lung cancer (NSCLC) mouse model that allows conditional expression of both $KRas^{G12D}$ and deregulated (inducible) Myc, the authors provide clear evidence that these two oncogenes collaborate with each other to instruct an immunosuppressive microenvironment that favors tumor growth and avoids immune recognition (1). In fact, quasi-physiological levels of Myc are able to turn indolent KRas-driven tumors into more aggressive, highly proliferative and inflammatory adenocarcinomas. As early as 24 hours post Myc activation, the authors observe a dramatic influx of $CD206^{+}$ tumor-associated macrophages to the tumor site, in striking contrast with an immediate T, B and NK cells exclusion. These stromal changes induced by Myc activation are due to the secretion of chemokine (C-C motif) ligand 9 (CCL9) and interleukin-23 (IL-23) by epithelial tumor cells. The importance of these two molecules is elegantly demonstrated by their co-blockade, which results in efficient reversion of all Myc-induced stromal changes and significant tumor shrinkage, explained by inhibition of tumor proliferation and induction of apoptosis. Specifically, CCL9 appears to be crucial for macrophage infiltration, angiogenesis and T cell loss, while IL-23 is responsible for T, B and NK cell exclusion, closely related to maintenance of Myc-driven lung tumors. Recruited macrophages express PD-L1 (independently of Myc activation), which is the main cause of T cell expulsion. Intriguingly, neither PD-L1 blockade nor CD4/CD8 had any therapeutic effect on KRas- and Myc-driven lung tumors, demonstrating the limited role of T cells in tumor maintenance. In contrast, by depleting $NK46^{+}$ cells, Kortlever and colleagues demonstrate that NK cells play an essential role in promoting tumor shrinkage upon Myc de-activation, which results in rapid tumor regression to indolent KRas-only adenomas and reversion of all Myc-induced stromal changes.

These findings elucidate a new aspect of the cooperation between KRas and Myc in tumorigenesis, while also revealing a new mechanism through which Myc favors an immunosuppressive tumor microenvironment. This evidence is nicely in line with another paper published at

the same time by Topper *et al.* also demonstrating that Myc expression has immunomodulatory effects *in vitro* in a panel of NSCLC cells lines as well as in both $KRas^{G12D}$-driven NSCLC and Lewis lung carcinoma (LLC) mouse models (2). In this case, the authors first show that epigenetic therapy with the DNA methyltransferase inhibitor (DNAMTi) azacitidine (aza) combined with the histone deacetylase inhibitor (HDACi) ITF-2357 was able to impair the growth of a panel of Ras-mutated NSCLC cell lines, upregulating interferon signalling pathways (including those associated with antigen presentation) and significantly downregulating Myc and Myc target genes. Similarly, in *in vivo* lung cancer models, treatment with the same epigenetic combination therapy reduced tumor burden, decreased Myc signaling pathways and triggered an anti-tumor immune response by inducing changes in immune populations. In the KRas-driven NSCLC model, epigenetic treatment reduced macrophage numbers and altered their angiogenic potential, while also facilitating $CD8^+$ T cell infiltration into lung tumors and reversing their exhausted phenotype to a more effector/memory one. Interestingly, in the LLC model, $CD8^+$ T cell depletion reduced the effect of the epigenetic therapy, suggesting a crucial role of these cells in mediating the therapeutic effect of the epigenetic treatment. The authors suggest that the recruitment of T cells to the tumor site is due to increased levels of CCL5 as a consequence of Myc downregulation by the epigenetic treatment (consistent with a repressing role of Myc over CCL5 transcription).

Interestingly, very early clinical trial data from the same group suggests that Myc status could become a potential biomarker of response to immune therapies in NSCLC, as the only patient that did not show durable clinical benefit in their study presented Myc amplification (3). Although very encouraging, these preliminary data should be validated in larger patient cohorts before being considered conclusive.

In summary, all these new findings highlight the importance of Myc in influencing the response to immunotherapies, which are now at the forefront of cancer treatment. These therapies, despite encouraging early results, are unfortunately effective only in a small percentage of patients, while the rest present intrinsic or rapidly acquired resistance, at least in part due to Myc deregulation. These new reports, together with previously published ones (4-7), are indisputable proof of Myc's role in directing an immunosuppressive tumor microenvironment through multiple different mechanisms, depending on tumor type, tissue and driving oncogenic lesions. To list some, these mechanisms include the activation and recruitment of tumor-associated macrophages (1,6,7), the expression of the immunosuppressive molecules CD47 and PD-L1 (4), the loss and exclusion of T, B and NK cells (1) and possibly even the modulation of immune cell metabolism itself (5). For these reasons, assessing Myc status prior to immunotherapy approaches could be informative regarding the potential benefit that patients could derive from such treatment.

Finally, one more implication of these studies is that new, up and coming anti-Myc therapies (8) may not only inhibit the direct oncogenic effects of Myc, but also antagonize the Myc-induced immunosuppressive microenvironment. This would create an ideal scenario where pre- or co-treatment with Myc inhibitors could trigger an immune-stimulatory environment favorable to immunotherapies, making our arsenal against cancer undoubtedly more powerful and effective.

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